1614

Contents:

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Title: Protamine-Free Insoluble Acylated Insulin Compositions

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(2) U.S. Claims

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Claims As Of 11/15/2001

1. Ultralente-like crystals, comprising:

a) a derivatized human insulin or derivatized human insulin analog formed by derivatizing human insulin or a human insulin analog with a saturated, straight-chain fatty acid having from 4 to 16 carbon atoms such that the fatty acid forms an amide bond with the ε-amino group of the B29-lysine of human insulin or a human insulin analog; and

b) a divalent metal cation.

2. The crystals of Claim 1, wherein the derivatized human insulin is selected from the group consisting of B29-butanoyl-human insulin, B29-pentanoyl-human insulin, and B29-hexanoyl-human insulin.

3. An insoluble composition, comprising the crystals of Claim 1.

4. The insoluble composition of claim 3, further comprising amorphous precipitate.

5. Ultralente-like crystals, comprising:

a) a protein selected from the group consisting of insulin and insulin analogs;

b) a derivatized human insulin or derivatized human insulin analog formed by derivatizing human insulin or a human insulin analog with a saturated, straight-chain fatty acid having from 4 to 16 carbon atoms such that the fatty acid forms an amide bond with the ε-amino group of the B29-lysine of human insulin or a human insulin analog; and

c) a divalent metal cation.

6. The crystals of Claim 5 , wherein the protein is human insulin.

7. The crystals of Claim 1, wherein the protein is a monomeric insulin analog.

9. The crystals of Claim 1, wherein the molar proportion of derivatized human insulin or derivatized human insulin analog is from 15% to 90% of the total protein.

10. The crystals of Claim 1, wherein the divalent metal cation is zinc, which is present at about 0.3 mole per mole of total protein to about 2 moles per mole of total protein.

11. An insoluble composition, comprising the crystals of Claim 5.

12. The insoluble composition of claim 11, further comprising amorphous precipitate.

13. A pharmaceutical composition, comprising an insoluble phase and a solution phase, wherein the insoluble phase comprises the insoluble composition of Claim 3 or 11, and wherein the soluble phase comprises an aqueous solvent.

14. The pharmaceutical composition of Claim 13 wherein the solution phase further comprises a preservative at a concentration of about 0.5 mg per mL to about 6 mg per mL of solution, a pharmaceutically acceptable buffer, and an isotonicity agent.

15. A method of treating diabetes comprising administering the crystals of Claim 1 or 5 to a patient in need thereof in a quantity sufficient to regulate blood glucose levels in the patient.

16. A method of treating diabetes comprising administering the insoluble composition of Claim 3 or 11 to a patient in need thereof in a quantity sufficient to regulate blood glucose levels in the patient.

17. A method of treating hyperglycemia comprising administering the crystals of Claim 1 or 5 to a patient in need thereof in a quantity sufficient to regulate blood glucose levels in the patient.

18. A method of treating hyperglycemia comprising administering the insoluble composition of Claim 3 or 11 to a patient in need thereof in a quantity sufficient to regulate blood glucose levels in the patient.

19. A process for preparing the crystals of Claim 1, comprising:

a) preparing a crystallization solution comprising the derivatized human insulin or derivatized human insulin analog, a buffer, a salt, and a divalent cation; and

b) allowing time for crystallization to occur.

20. A process for preparing the crystals of Claim 5, comprising:

a) preparing a crystallization solution comprising (i) a protein, (ii) a derivatized human insulin or derivatized human insulin analog, (iii) a buffer, (iv) a salt, and (v) a divalent cation;

b) combining the crystallization solution of a) with a nucleating seed suspension; and

c) allowing time for crystallization to occur.

21. The crystals of Claim 1, wherein the fatty acid is myristoyl fatty acid.

22. The crystals of Claim 1, wherein the fatty acid is n-octanoic fatty acid.

23. The crystals of claim 1, wherein the human insulin analog is des(ThrB30)-human insulin.

24. The crystals of Claim 5, wherein the fatty acid is myristoyl fatty acid.

25. The crystals of claim 5, wherein the fatty acid is n-octanoic fatty acid.

26. The crystals of claim 5, wherein the human insulin analog is des(ThrB30)-human insulin.

27. The crystals of Claim 5, wherein the molar proportion of derivatized human insulin or derivatized human insulin analog is from 15% to 90% of the total protein.

28. The crystals of Claim 5, wherein the divalent metal cation is zinc, which is present at about 0.3 mole per mole of total protein to about 2 moles per mole of total protein.